

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 15830

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

10 SEP 2005

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/032771

International filing date (day/month/year)
28.10.2004

Priority date (day/month/year)
10.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07D265/30, C07D413/06, A61K31/5375, A61K31/5377, A61P25/22

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/032771

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 27,28

because:

- ☒ the said international application, or the said claims Nos. 27,28 (Industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------------|
| Novelty (N) | Yes: Claims | 1-30,33,34 |
| | No: Claims | 31,32 |
| Inventive step (IS) | Yes: Claims | 1-30,33,34 |
| | No: Claims | 31,32 |
| Industrial applicability (IA) | Yes: Claims | 1-26,29-34 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

III NON-ESTABLISHMENT

Claims 27,28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Functional definitions such as "protecting group" are not clear (see claims 29-32);

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

- D1: WO 03/018576 A (ASTRAZENECA AB; GUSTAFSSON, JOERGEN; HOSSAIN, NAFIZAL; NILSSON, STINAB) 6 March 2003 (2003-03-06)
- D2: WO 01/00214 A (MERCK & CO., INC; HUNT, JULIANNE, A; MILLS, SANDER, G; SINCLAIR, PETER) 4 January 2001 (2001-01-04)
- D3: KING, FRANK D. ET AL: "The synthesis of 2-morpholinecarboxylic acid derivatives and their elaboration to 1-aza-4-oxabicyclo[3.3.1]nonan-6-one" TETRAHEDRON LETTERS , 32(20), 2281-4 CODEN: TELEAY; ISSN: 0040-4039, 1991, XP002317574
- D4: WO 01/01973 A (PHARMACIA & UPJOHN COMPANY; WONG, ERIK, H., F; AHMED, SAEEDUDDIN; MARS) 11 January 2001 (2001-01-11)
- D5: WO 99/37305 A (GLAXO GROUP LIMITED; MORGAN, PHILLIP, FREDERICK; MUSSO, DAVID, LEE; PA) 29 July 1999 (1999-07-29)

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 31,31 is anticipated by D1-D3 (see for passages in the ISR. (Article 33(2) PCT).

The claimed subject-matter of the remaining claims is considered to be novel. The essential structural difference between the claimed compounds and those of the prior art resides in the presence of the specific substituent in position 2 of the morpholine unit.

3. INVENTIVE STEP

The subject-matter of the novel claims appears to fulfil the requirements of Article 33(3) PCT for the following reasons:

The closest state of the art for the present application is represented by D4 and D5. Said documents deal with reuptake inhibitors. The compounds of D4 and D5 differ as explained under item novelty.

The problem of the present application may be seen in the provision of further substituted morpholines acting as norepinephrine reuptake inhibitors, and therefore being useful in the treatment of diseases/disorders such as anxiety and hyperactivity

Neither D4 or D5 nor the combination of the two teach the structural variation necessary in order to arrive at the presently claimed compounds.

Accordingly the presently claimed solution does not appear to be obvious. It is proofed in the description the problem is actually solved. In a regional phase it might become necessary to indicate at least one tested compound in order to allow an assessment of the plausibility of the generalisation of claim 1.

The novel intermediates contribute structurally to the products.

Accordingly inventive step can in principle be acknowledged.

VI CERTAIN DOCUMENTS CITED

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/032771

- D6: FR-A-2 852 954 (AVENTIS PHARMA SA) 1 October 2004 (2004-10-01)
D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS,
OHIO, US; KATO, SHIRO ET AL: "1-(1-Substituted-4-piperidinylmethyl)pipe
ridine derivatives as 5-TH4 receptor agonists, pharmaceutical compositions
containing them, and their use" XP002317575 retrieved from STN Database
accession no. 2004:819908
D8: WO 2004/018441 A (ELI LILLY AND COMPANY; CASES-THOMAS,
MANUEL, JAVIER; HAUGHTON, HELEN,) 4 March 2004 (2004-03-04)

D6-D8 might become highly relevant documents in the regional phase.